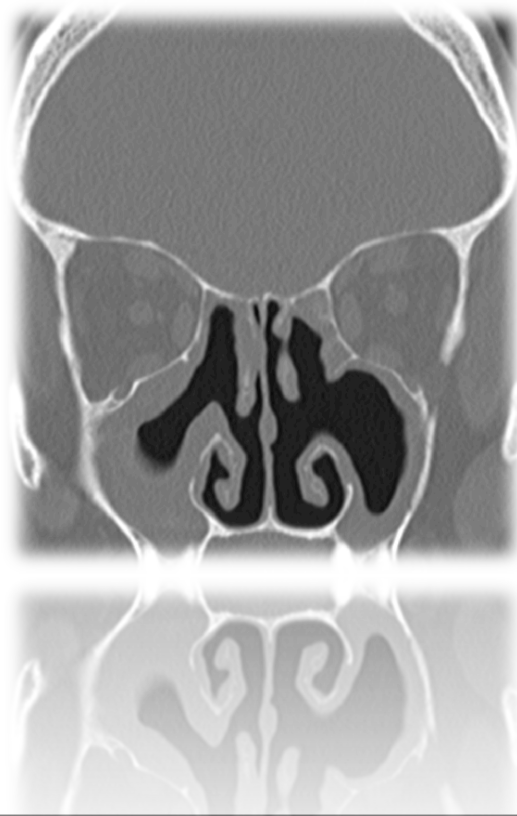


TARGETING POST-SURGICAL STAPHYLOCOCCUS AUREUS IN CHRONIC RHINOSINUSITIS

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Cover image:

Axial non-contrast CT image of a 54 yo female patient with surgically-recalcitrant chronic rhinosinusitis, with maxillary sinus mucosal thickening evident. *Staphylococcus aureus* is frequently cultured from swabs taken from both her maxillary sinuses.

To my darling Maggie, the kindest person I know

Declaration

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Dr. Josh Jervis-Bardy

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Jervis-Bardy J, Foreman A, Bray S, Tan L, Wormald PJ.

Laryngoscope 2011;121:1104-7.

What is the origin of Staphylococcus aureus in the postoperative sinonasal cavity?

Jervis-Bardy J, Foreman A, Boase S, Valentine R, Wormald PJ.

International Forum of Allergy and Rhinology 2011;1:308–312.

Microbiological outcomes following mupirocin nasal rinses for symptomatic, Staphylococcus aureus-positive chronic rhinosinusitis following endoscopic sinus surgery.

Jervis-Bardy J, Wormald PJ.

International Forum of Allergy and Rhinology 2012;2:111-5.

A randomised trial of mupirocin sinonasal rinses versus saline in surgically-recalcitrant staphylococcal chronic rhinosinusitis.

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The in vitro activity of Manuka Honey on S. aureus biofilms is time and dose dependent: Potential implications for treatment of persistent mucosal infection following endoscopic sinus surgery.

Australian Wound Management Association ASM, Perth, March 2010.

Methyloglyoxal-infused honey mimics the anti-S. aureus biofilm activity of Manuka Honey: Potential implications in Chronic Rhinosinusitis.

Australasian Rhinological Society ASM, Sydney, September 2010.

The etiology of sinonasal Staphylococcus aureus following surgery for Chronic Rhinosinusitis.

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Understanding CRS and novel topical therapies.

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Microbiological outcomes following Mupirocin nasal rinses for symptomatic, S. aureus-positive Chronic Rhinosinusitis following endoscopic sinus surgery.

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15th Advanced Functional Endoscopic Sinus Surgery Course, Adelaide, November 2011.

Mupirocin nasal rinses versus placebo in recalcitrant, Staphylococcus aureus-positive chronic rhinosinusitis: a randomised controlled trial.

Australasian Society of Otolaryngology Head & Neck Surgery ASM, Adelaide, April 2012.

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Abbreviations used in this thesis

AFRS	Allergic fungal rhinosinusitis
ATCC	American Type Culture Collection
CAZS	Citric acid/Zwitterionic surfactant
CRS	Chronic Rhinosinusitis
CRSsP	Chronic Rhinosinusitis <i>sans</i> (without) polyposis
CRSwP	Chronic Rhinosinusitis with polyposis
CSF	Cerebrospinal fluid
EDTA	Ethylenediaminetetraacetic acid
EM	Eosinophilic mucous
EML	Endoscopic modified Lothrop
ESS	Endoscopic sinus surgery
FDA	Federal Drug Authority
FESS	Functional endoscopic sinus surgery
FISH	Fluorescence <i>in situ</i> hybridisation
HIV/AIDS	Human immunodeficiency virus/Acquired immunodeficiency syndrome
IQR	Inter-quartile range
MGO	Methylglyoxal
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NIR	Near infra-red
PMN	Polymorphonuclear
RCT	Randomized controlled trial
SNOT-20	Sino-Nasal Outcome Test (20)
SW	Shock-wave
TGA	Therapeutic Goods Administration
VAS	Visual analogue scale

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Thesis summary

The research contained within this thesis is an investigation of topical antimicrobial treatments in a subset of patients with Chronic Rhinosinusitis (CRS). For the purposes of this manuscript, our 'patient of interest' has persistent disease following sinus surgery ('surgically-recalcitrant disease') and a sinonasal cavity that similarly persistently cultures *Staphylococcus aureus*.

To begin with, an extensive literature review is presented in three parts. Firstly, the definition, epidemiology, socioeconomic burden, aetiopathogenic theories and the management of CRS are discussed. From the literature review, it is clear that CRS is disease without a unifying, underlying aetiopathogenic factor, nor does there exist a universal panacea for the treatment of the surgically-recalcitrant patient. Of promise, however, recent research suggests that there may be merit in aggressively targeting the presumed *S. aureus* biofilm bioburden in these patients with topical antimicrobials. Secondly, therefore, we progressed to explore the myriad of possible antimicrobial agents for use as topical treatments in CRS. This exhaustive list includes a number of anti-biofilm strategies that have unknown treatment potential in CRS, as many have not previously been mentioned, let alone evaluated, in the Rhinological literature to-date. Thirdly, recognizing the importance of device selection in delivering topical treatment to the sinuses, we reviewed the potential delivery modalities currently available for this purpose.

The research investigation commenced with two studies evaluating the efficacy of mupirocin sinonasal rinses in recalcitrant *S. aureus*-positive CRS. Following from two small studies reported in the literature, we felt it was important to firstly evaluate this treatment in a prospective randomized control trial, and secondly, to retrospectively assess a much larger cohort. The former study revealed that mupirocin treatment was greatly superior compared to placebo in removing culturable *S. aureus* from the sinuses. Additionally, it improved both the endoscopic appearance of the sinonasal cavity and patient-reported symptoms

following treatment, although only the endoscopic examination results were significantly different when compared to those observed in the placebo arm. The latter study demonstrated that long-term, well after the mupirocin treatment is complete, *S. aureus* is again readily cultured in these patients; it appears, therefore, that whilst mupirocin is a promising treatment, there is a significant rebound following cessation of treatment. We also determined that thankfully, however, the rate of induced resistance mupirocin is very low.

The third study performed was an in vitro assessment of the anti-biofilm activity of Manuka (*Leptospermum scoparium*) honey. In this study we demonstrated that Manuka honey is not active against *S. aureus* biofilms at concentrations amenable to delivery using a rinse bottle; however, there is sufficient activity when Manuka honey is fortified with exogenous methylglyoxal (MGO). MGO has recently been identified as the active constituent in Manuka honey. These findings are significant, because Manuka honey may be suitable as a long-term treatment option by virtue of its excellent resistance profile. Whereas fears of inducing treatment-resistant bacterial strains limit the long-term use of traditional antibiotics (such as mupirocin), Manuka honey may be a suitable long-term or even maintenance therapy in surgically-recalcitrant *S. aureus*-positive CRS.

Our final study aimed to evaluate the origins of sinonasal *S. aureus* following sinus surgery, as previous studies have shown culture rates of this organism to increase in the post-operative period. We had previously hypothesized that this increase in culture-rate may be a result of biofilm activity. In this current study, we indeed identified biofilm dispersal as the likely underlying causal factor. As a result, we now further suggest that the early post-operative period may be an ideal treatment window in which to treat with antimicrobials given the vulnerable state of the dispersed biofilm during this time. Rather than being a *treatment agent* study like the other papers in this thesis, this *treatment time* evaluation may ultimately precipitate early anti-biofilm intervention trials in the future.